**Dipyridamole dilates large coronary arteries in conscious dogs**

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**ABSTRACT**  The effects of 0.25 mg/kg dipyridamole on left ventricular (LV) pressures, LV dP/dt, heart rate, aortic pressures, left circumflex coronary blood flow, and left circumflex coronary arterial diameters and on calculations of late diastolic coronary resistance and large coronary cross-sectional area were studied in 15 conscious dogs. Injection of dipyridamole, a drug that has a mechanism of action dependent on myocardial adenosine production, caused sustained increases in mean coronary blood flow (244 ± 28%), large coronary arterial cross-sectional area (28 ± 3.2%), heart rate (32 ± 3.6%), and LV dP/dt (23 ± 3.0%) and reductions in late diastolic coronary resistance (73 ± 2.4%) and mean arterial pressure (14 ± 1.9%). Neither β-adrenergic–receptor blockade alone nor in conjunction with constant heart rate affected the dilation of large coronary arteries to dipyridamole significantly. Ganglionic blockade with hexamethonium also had little effect on the response of large and small coronary vessels to dipyridamole. Surprisingly neither β-adrenergic–receptor nor ganglionic blockade abolished the rise in LV dP/dt observed after dipyridamole. Aminophylline, however, effectively eliminated the dilation of large coronary arteries and resistance coronary vessels in response to dipyridamole. In summary, as long as dipyridamole does not induce severe sustained hypotension it exerts potent effects on both coronary arterial resistance and large coronary arteries in the conscious dog. The coronary dilation is independent of reflex adrenergic activation, but appears dependent on myocardial adenosine production.

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flex coronary artery with 5-0 suturing (Ethicon, Inc., Somerville, NJ). Alignment of the crystals was maximized at surgery by monitoring the transmitted ultrasonic signal with an oscilloscope. In 10 of the dogs a Doppler ultrasonic (n = 9) or electromagnetic (n = 1) flow transducer was implanted distally on the same vessel.

Arterial and left atrial pressures were measured with the implanted catheters attached to Statham P23Db strain-gauge manometers (Statham Instruments, Inc., Oxnard, CA). Left ventricular (LV) pressure was measured with the implanted solid-state transducers. These transducers were calibrated in vitro against a mercury manometer and cross-calibrated in vivo with pressures recorded from the arterial and left atrial catheters. Instantaneous and continuous measurements of external left circumflex coronary arterial diameter were obtained with an improved ultrasonic transit-time dimension gauge. The instrument measures dimensions by generating a voltage linearly proportional to the transit time of acoustic impulses traveling at the sonic velocity of 1.55 mm/μsec in tissue. The dimension gauge was modified to allow measurement of small dimensions in the arterial system. Any drift in the dimension gauge, tape recording system, or the strip chart recorder were eliminated by frequent calibration during the experiment. The received ultrasonic dimension signal was monitored continuously during the experiment with an oscilloscope. Coronary blood flow was measured with a Benton Square wave electromagnetic flow meter (Benton Instruments, Cupertino, California) or a Doppler flow meter. Any flow reference was established by transient coronary occlusion with a hydraulic occluder. The Doppler flow meter has a reliable zero reference.

Experiments were conducted 1 to 3 weeks after surgery when the animals were healthy and had been trained to lie on the table. After control measurements of arterial and LV pressures, heart rate, LV dP/dt, coronary blood flow, and coronary diameter were recorded, 0.25 mg/kg iv dipyridamole (Persantine; Boehringer Ingelheim, Inc., Tarrytown, NY) was injected and recordings were continued for 60 min. Another dose of dipyridamole was given to 10 dogs either 1 to 2 hr later or on a separate day after propranolol alone and to seven dogs on another day after they had received propranolol and while their heart rates were held constant by electrical pacing. On a separate occasion in six dogs dipyridamole was injected after aminophylline (1.0 mg/kg/min for 10 min) and in the presence of β-adrenergic receptor blockade. Aminophylline was administered after β-adrenergic receptor blockade to prevent any complicating increases in myocardial metabolic demand and thus secondary dilatation of large coronary arteries, which might have obscured the large coronary dilating effect of dipyridamole. The adequacy of β-adrenergic receptor and adenosine-receptor blockade were checked by injection of 0.1 μg/kg isoproterenol and 0.47 μM/kg adenosine, respectively. On a separate day 0.25 mg/kg dipyridamole was injected into four dogs after ganglionic blockade with 30 mg/kg hexamethonium. Dipyridamole was also administered to two open-chest dogs anesthetized with 30 mg/kg pentobarbital Na.

Data were recorded continuously on magnetite tape (Bell and Howell, Inc., Datatape Division, Pasadena, CA) and played back on a multichannel ink recorder (Gould-Brush, Cleveland, OH). Mean pressures and coronary diameters were derived with the use of R-C filters with a 2 sec time constant. LV dP/dt was derived from the LV pressure signal with Philbrick operational amplifiers (Teledyne Philbrick, Dedham, MA; frequency response of 700 Hz) connected as differentiators. A triangle wave was substituted for the pressure signal to calibrate the differentiator directly. Heart rate was measured with a cardiotachometer (Beckman Instruments) triggered by the LV pressure pulse. Internal coronary cross-sectional area (CSA) was calculated with known wall volume, blood vessel density, mass of the artery, and instantaneous external diameter. Late diastolic coronary resistance (LDCR), an index of changes in resistance coronary vessels, was calculated as the quotient of late diastolic aortic pressure and late diastolic coronary blood flow. Statistical analysis was performed by analysis of variance.

Results

Baseline values are listed in the tables and figures.

Effects of 0.25 mg/kg dipyridamole. The effects of dipyridamole on phasic changes in coronary blood flow and diameter are shown in figure 1, and the average changes for the entire group of dogs studied are shown in figure 2. The maximal increase in coronary blood flow occurred 35 ± 4.0 sec after dipyridamole, while maximal increases in coronary diameter occurred 127 ± 11 sec after dipyridamole (figure 2). The maximal changes from control for all the variables are listed in table 1. In summary, dipyridamole reduced mean arterial pressure by 14 ± 1.9%, LV systolic pressure by 5.1 ± 1.2%, and LV end-diastolic pressure by 20 ± 4.3% and increased heart rate by 32 ± 3.6%, LV dP/dt by 23 ± 3.0%, mean coronary blood flow by 244 ± 28%, mean coronary diameter by 6.6 ± 0.7%, and CSA by 28 ± 3.2%, while LDCR fell by 73 ± 2.4%. All these changes were significant (p < .01).

Effects of dipyridamole after β-blocking drugs. The changes in large coronary arterial CSA, mean arterial pressure, and LDCR after β-adrenergic–receptor blockade are shown in figure 2. There were no significant differences from the unblocked group.

The responses in the seven dogs with constant heart rates in the presence and absence of β-adrenergic–receptor blockade are compared in figures 3 and 4. Dipyridamole reduced mean arterial pressure by 13 ± 1.4% and LV systolic pressure by 4.2 ± 1.8, and increased LV dP/dt by 21 ± 3.3%, values similar to those observed without blockade (figure 3). Heart rate and LV end-diastolic pressure did not change. Coronary blood flow, coronary diameter, and CSA increased by 163 ± 20%, 3.94 ± 0.89%, and 17 ± 3.8%, while LDCR fell by 56 ± 6.3%. The increases in CSA were not statistically significant, while the decreases in LDCR were significantly less (p < .02) after β-adrenergic blockade. It is important to note that baseline values were different and that LDCR actually fell to the same level under both conditions. Thus, holding heart rate constant and administering β-adrenergic blockers induced slight alterations from baseline, but failed to induce major differences in the response to dipyridamole.

After ganglionic blockade with hexamethonium in four dogs dipyridamole still reduced mean arterial pressure 26 ± 4.0% from 99 ± 6.1 mm Hg and
increased LV dP/dt by $21 \pm 4.5\%$ from $2228 \pm 139$ mm Hg/sec, while heart rate did not change from a control of $148 \pm 4.0$ beats/min. Mean coronary blood flow increased by $161 \pm 42\%$ from $27 \pm 2.2$ ml/min, while coronary diameter increased by $6.2 \pm 0.7\%$ from $3.47 \pm 0.30$ mm and CSA increased by $26 \pm 2.9\%$ from a control of $4.73 \pm 0.88$ mm$^2$. LDCR fell by $67 \pm 6.5\%$ from $2.58 \pm 0.29$ mm Hg/ml/min.

After aminophylline in six dogs the dilation of large coronary arteries, the reductions in arterial pressure,
and LDCR and the increases in CSA were markedly reduced not only in magnitude, but more impressively in duration (figure 2).

**Effects of 0.25 mg/kg dipyridamole during anesthesia.**

During pentobarbital anesthesia and left thoracotomy in two dogs, dipyridamole caused a small fall in CSA of 6.9 ± 1.0% from 6.33 ± 2.68 mm². This is contrast to the large increases in CSA that normally occur in response to dipyridamole in the conscious dog.

**Discussion**

The results of our experiments in normal, conscious dogs indicate that dipyridamole is a potent dilator of large coronary arteries as well as of coronary resistance vessels. The fact that dipyridamole elicits near-maximal decreases in coronary vascular resistance is consistent with the work of other investigators who used a variety of experimental techniques1, 2, 5-9, 10, 20, 21 and with the proposed site of action of adenosine.22 Adenosine exerts its primary effects on small coronary resistance vessels and thus may regulate the increases in coronary flow that accompany an increase in myocardial metabolic demand.12 However, the effects of dipyridamole on large coronary arteries is much more controversial. Most prior studies in anesthetized open-chest animals5-9 or in man, in which normal segments of large coronary arteries distal to a stenosis were studied,10 indicated that dipyridamole did not dilate large coronary arteries. One study conducted in isolated coronary strips did demonstrate a relaxing effect of dipyridamole on large coronary arteries,23 while in another only a relatively small effect was observed.24 We also found that dipyridamole did not increase large coronary vessel CSA in two anesthetized open-chest dogs. Recently Noguchi et al.,9 using the same techniques in anesthetized open-chest dogs, found a reduction in large coronary arterial dimensions with dipyridamole. The difference between the results in conscious and anesthetized animals may be due to a direct or indirect effect of anesthesia on vascular smooth muscle tone25, 26 or to an indirect effect of the high resting heart rate and secondary large coronary arterial dilation ob-

**FIGURE 2.** The average (± SEM) effects of 0.25 mg/kg dipyridamole are shown as percent changes in left circumflex coronary CSA, mean arterial pressure (MAP), and LDCR before (circles and solid lines) and after β-adrenergic-receptor blockade (squares and dotted lines). β-Adrenergic-receptor blockades had no significant effect on either the peak or the duration of the response to dipyridamole. After aminophylline (triangles and broken lines) the sustained effects of dipyridamole on the coronary circulation were essentially blocked.

| TABLE 1 |
| Effects of 0.25 mg/kg dipyridamole |

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Control</th>
<th>Peak changes from control*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>15</td>
<td>100 ± 2.7</td>
<td>-13.9 ± 1.9</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>15</td>
<td>83 ± 3.9</td>
<td>+27 ± 3.3</td>
</tr>
<tr>
<td>Left ventricular pressure (mm Hg)</td>
<td>14</td>
<td>127 ± 3.2</td>
<td>-6.7 ± 1.6</td>
</tr>
<tr>
<td>LV end-diastolic pressure (mm Hg)</td>
<td>11</td>
<td>8.1 ± 0.7</td>
<td>-1.5 ± 0.37</td>
</tr>
<tr>
<td>LV dP/dt (mm Hg/sec)</td>
<td>14</td>
<td>3517 ± 127</td>
<td>+809 ± 106</td>
</tr>
<tr>
<td>Mean coronary blood flow (ml/min)</td>
<td>10</td>
<td>28 ± 2.2</td>
<td>+64 ± 6.1</td>
</tr>
<tr>
<td>LDCR (mm Hg/ml/min)</td>
<td>10</td>
<td>2.83 ± 0.28</td>
<td>-2.08 ± 0.24</td>
</tr>
<tr>
<td>Coronary diameter (mm)</td>
<td>14</td>
<td>4.12 ± 0.21</td>
<td>+0.26 ± 0.03</td>
</tr>
<tr>
<td>Coronary CSA (mm²)</td>
<td>15</td>
<td>6.75 ± 0.69</td>
<td>+1.79 ± 0.21</td>
</tr>
</tbody>
</table>

*All values are different from control, p < .01.
The possibility that the dilation of large coronary arteries induced by dipyridamole was due to increases in myocardial metabolic demand secondary to reflex increases in heart rate and LV dP/dt was considered. To test this possibility, dipyridamole was injected on one occasion after β-adrenergic–receptor blockade alone, on another after β-adrenergic–receptor blockade, and with heart rate constant, and on another after ganglionic blockade with hexamethonium. Under all these conditions the drug had effects on large coronary arteries and on resistance vessels very similar to those observed in the experiments performed in the absence of blockade. Thus, as expected, the mechanism of coronary dilation induced by dipyridamole did not involve reflex adrenergic effects. However, it was surprising that the increases in LV dP/dt with dipyridamole were not prevented by either β-adrenergic or ganglionic blockade. The persistent effects of dipyridamole on LV dP/dt could not be attributed to inadequate blockade.
equate β-adrenergic blockade. For example, the increases in LV dP/dt after 0.1 μg/kg isoproterenol (121 ± 21%) were essentially abolished (14 ± 3.2%) after β-adrenergic-receptor blockade, yet the rise in LV dP/dt in response to dipyridamole was virtually unaffected. Thus, the increase in LV dP/dt induced by dipyridamole is probably not the result of activation of either autonomic reflexes or the sympathetic nervous system, but rather a direct effect. The results of prior work on the effects of adenosine on myocardial contractility have been conflicting.27 However, it is interesting to note that a pyrimidinylpyrimidine derivative (ARL-115), which has a structure similar to that of dipyridamole, has been shown to exert direct positive inotropic activity independent of adrenergic or other reflex effects in anesthetized and conscious dogs.28,29

Dipyridamole is thought to inhibit the uptake of adenosine and thereby potentiate the activity of this powerful endogenous coronary vasodilator. Afonso3 and Afonso and O’Brien1 found that the coronary dilating action of dipyridamole and adenosine were inhibited by aminophylline and that dipyridamole potentiated the vasodilating action of adenosine triphosphate. Küberl et al.4 found that dipyridamole inhibited the degradation of adenosine to inosine by blocking its penetration into myocardial cells, whereas Nott3 found that dipyridamole potentiated the heart block caused by adenosine at low doses by inhibiting adenosine uptake or, at high doses, by also inhibiting adenosine deamination. Furthermore, Kalsner20 found that dipyridamole directly inhibited the uptake of adenosine into coronary blood vessels. Prior studies have also indicated that vasodilatation of coronary resistance vessels in response to dipyridamole is blocked by the methylxanthines, since the mechanism of vasodilation involves adenosine.1-4,24 Consistent with the findings of these prior studies, we observed that the effects of dipyridamole on resistance coronary vessels were largely eliminated by the preadministration of aminophylline. Furthermore, we found that the dipyridamole-induced dilation of large coronary arteries was blocked by aminophylline.

It is conceivable that the dilation of large coronary arteries is in part secondary to the large increases in coronary blood flow that occur after the administration of dipyridamole. In prior studies in which a large atrioventricular shunt was opened in the femoral circulation a dramatic flow-dependent increase in large arterial dimensions was observed.30,31 Gerova et al.32 found large coronary artery dilation when flow increased markedly with opening of an atrioventricular shunt. We have recently observed that the reactive dilation of large coronary arteries after brief periods of coronary occlusion and myocardial ischemia can be eliminated by preventing reactive hyperemia on release of the coronary occlusion; however, the increase in large coronary arterial dimensions secondary to increasing heart rate or adenosine administration is only partially attenuated by this technique.33 It is unlikely that the mechanism of the large coronary arterial dilation in our study was due to the increased flow velocity only since in previous studies in anesthetized animals marked increases in coronary blood flow occurred with dipyridamole, yet the resistance of large coronary arteries5-8 and large coronary artery diameter9 were not changed by the drug.

The deleterious actions of dipyridamole in the presence of regional myocardial ischemia have been attributed to its prominent effects on small coronary vessels, which result in a massive fall in resistance in the nonischemic zone and diversion of blood flow from the ischemic area.6,7 Since coronary collateral channels are thought to behave like large coronary arteries, and some prior studies failed to observe large coronary arterial dilation with dipyridamole,5-9 it was postulated that dipyridamole elicits a "steal" by dilating coronary resistance vessels and not the large collateral vessels that are crucial in maintaining blood flow to ischemic myocardium. Studies by Winbury et al.34 and Weiss and Winbury35 have suggested that dipyridamole does not increase oxygen delivery to the endocardium, as opposed to nitroglycerin, which has this favorable effect. Dipyridamole also does not increase retrograde coronary flow.36 These studies were also conducted in anesthetized animals. In contrast, studies by Rembert et al.21 in conscious dogs have shown that dipyridamole shifted the distribution of blood flow to the endocardium.

Since our experiments were conducted in healthy, conscious dogs, it is difficult to extrapolate our results to the situation of regional myocardial ischemia. However, a recent study by Blumenthal et al.37 showed that dipyridamole reduced experimental infarct size considerably, and that this was attributable to an increase in coronary collateral flow as measured with the radioactive microsphere technique. These authors believe that in previous studies with dipyridamole exacerbation of myocardial ischemia resulted, due primarily to the large fall in coronary perfusion pressure caused by an excessive dose of dipyridamole. Indeed, aortic pressure is a principal determinant of coronary collateral blood flow38 and transmural myocardial perfusion.39 The reduction in mean arterial pressure observed and the dose of dipyridamole used in the study.
by Blumenthal et al. are similar to those in our study and in other studies in man. Thus, the extent of reduction in coronary perfusion pressure could well be the critical factor in determining whether dipyridamole dilates large coronary arteries and collateral channels.

In summary, dipyridamole dilates large and small coronary resistance vessels in the conscious dog. These actions are exclusive of changes in myocardial metabolic demand or \(\beta\)-adrenergic mechanisms, but appear dependent on the production of adenosine. If the collateral channels behave as large coronary arteries and if the responses in the presence of ischemic heart disease are similar to those in the normal animal, then any potential deleterious effect of dipyridamole in the ischemic setting must be explained by some mechanism other than failure to dilate large coronary arteries.

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References


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